Haemoglobin A1c or Glycated Albumin for Diagnosis and Monitoring Diabetes: An African Perspective

J. A. George¹ · R. T. Erasmus²

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Abstract Diabetes mellitus (DM) has reached epidemic proportions across the globe with the largest increases seen in sub-Saharan Africa. Those that are diagnosed are largely poorly controlled. This review summarizes the limitations of the use of glycated haemoglobin (HbA1c) in Africa and current knowledge on the utility of glycated albumin and fructosamine in African patients. The diagnosis and monitoring of DM in African patients may be compromised by associated conditions like sickle cell anaemia, chronic kidney disease and HIV infection. Glycated albumin reflects short term glycaemia and is not affected by many conditions that alter HbA1c. It can be measured enzymatically, and this review discusses methods for analysis, and discusses the advantages and limitations in specific situations with an emphasis on conditions that also affect HbA1c.

Keywords HbA1c · Diabetes · Glycated albumin · Fructosamine

Introduction

In Sub-Saharan Africa the numbers of people with type II diabetes (T2D) are expected to increase from 14.2 million in 2015 to 34.2 million by 2040 with almost 70% of people with T2D undiagnosed [1]. The results of the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) demonstrated that importance of tight glucose control for the prevention of complications of diabetes and of HbA1c as an indicator of mean glycaemia [2]. Early diagnosis and monitoring are therefore critical to delay the onset of complications. Although glucose measurement, either fasting or 2 h post prandial, is considered the gold standard for diagnosis it is subject to several limitations. This led to a search for alternatives such as haemoglobin A1c (HbA1c) which can be used both for monitoring and diagnosis [3].

Haemoglobin A1C is formed by the non-enzymatic glycation of haemoglobin and represents a measure of the glucose concentration over the last 2–3 months. Glycation is the non-enzymatic attachment of a reducing sugar to primary or secondary amine groups to form an intermediate Schiff base followed by more stable ketoamine derivatives, the Amadori products, which in turn undergo further rearrangements to form a heterogeneous group of compounds called advanced glycation end products (AGEs) [4]. Fructosamine (FA) and glycated albumin (GA) are also products of this reaction that have been adapted into clinical practice for use in assessing control.

✉ J. A. George
Jaya.george@wits.ac.za

¹ Department of Chemical Pathology, National Health Laboratory Services and University of Witwatersrand, Johannesburg, South Africa

² Department of Chemical Pathology, National Health Laboratory Services and University of Stellenbosch, Stellenbosch, South Africa

Glycated Albumin and Fructosamine

Albumin is the most abundant circulating plasma protein with plasma concentrations ranging between 35 and 55 g/L. It is made up of a single polypeptide chain with an abundance of lysine and arginine residues. It is these that make it particularly susceptible to glycation. Glycated albumin is considered an intermediate marker of glycaemia because the turnover of albumin is shorter than the lifespan of erythrocytes (20 vs. 120 days). Glycated albumin measures only serum albumin, which accounts for over 80% of serum glycated proteins and is defined either as the ratio of glycated albumin molecules to total albumin molecules or as the ratio of glycated albumin amino acids to total albumin. It is measured by colorimetry, spectroscopy, enzymatic assays, immunoassays, high pressure liquid chromatography (HPLC) or mass spectrometry (MS). Not only are these methods different, but each method may measure different glycation sites. In an effort to achieve standardization, the Committee on Diabetes Mellitus Indices of the Japan Society of Clinical Chemistry has developed an isotope dilution liquid chromatography/tandem mass spectrometry method as a reference measurement procedure, and a certified reference material (JCCRM611), for glycated albumin measurement [5]. A U.S. Food and Drug Administration—approved method for glycated albumin measurement manufactured by Diazyme Laboratories (Poway, CA) is commercially available [6], but the glycated albumin assay developed by Asahi Kasei in Japan, is the method most widely used globally and most extensively evaluated in clinical studies [7].

Fructosamine (FA) refers to all ketoamine linkages that result from glycation of plasma proteins. A method for measuring FA was developed in the 1980s based on the ability of serum fructosamines to reduce nitroblue tetrazolium (NBT) and change the dye's absorbance [8]. The test for serum fructosamine is simpler and less costly than that for HbA1c, but at present is less frequently used. More recently, enzymatic assays for measuring FA have been described. Some of the current assays for FA are Food and Drug Administration and have documented good performance [9]. Because FA is expressed as reducing ability per mL of serum, it is influenced by serum protein concentration, and an apparently low level of FA is observed in blood dilution related anemia and high concentrations are seen for example in myeloma. Furthermore, colorimetric assays are prone to interference by reducing substances such as uric acid, bilirubin and hypertriglyceridemia.

The use of HbA1c is for the diagnosis and monitoring of diabetes is appealing for a number of reasons. It is not subject to pre-analytical variation to the same extent that blood glucose is. It is not affected by acute stress induced

hyperglycaemia, and measurement has been standardized with efforts to standardize reporting as well. On the other hand, factors such as age, drugs and haemolytic anaemias may affect HbA1c. Furthermore HbA1c has limited ability to reflect short-term glycaemic changes, and it cannot reveal postprandial hyperglycaemia (high blood sugars straight after a meal) and fasting hyperglycaemia separately. These parameters are not to be neglected, as a growing body of evidence suggests that postprandial hyperglycaemia and glycaemic variability may be independent risk factors for macro vascular complications in patients with diabetes [10]. Although HbA1c is useful in the vast majority of patients, there are some situations where an alternative is preferable.

The American Diabetes Association (ADA) states that FA may be a better choice when HbA1c cannot be reliably measured such as in situations where there is shortened red cell lifespan such as haemolytic anaemias, and in pregnancy, since the glucose and insulin needs of the mother and foetus change rapidly during gestation.

However in addition to these disease conditions there are several other disease states that are very prevalent in Africa that affect the clinical utility of HbA1c and for which alternate markers may be necessary. These include chronic renal failure, HIV and tuberculosis. Some of these are discussed in the following section. In addition ethnicity and body mass index may influence concentrations. These are discussed in further detail below.

Anaemia

Anaemia is a major public health problem affecting 1.6 billion people worldwide [11] with the problem being greater in pregnancy and in childhood [12]. Haemoglobin A1C is modified by anaemia independent of glycaemic status because glycation of red cells is slower in new cells.

Genetic variants e.g. HbS trait, HbC trait, and elevated fetal hemoglobin (HbF) interfere with the measurement of HbA1c. The inherited beta thalassemias including sickle cell anemia and hemoglobin E (HbE) disorders are most prevalent in certain malaria prone parts of the world including Africa, all Mediterranean countries, the Middle East, the Indian subcontinent and Southeast Asia and with globalization these disorders are increasingly seen in previously non-endemic areas [13].

Less common haemoglobin variants may also cause interference as well as any condition that shortens erythrocyte survival or decreases mean erythrocyte age e.g., recovery from acute blood loss and hemolytic anemia. These interferences are method dependent and details of these are available on the National Glycohaemoglobin Standardization website [14]. Glycated albumin is not

affected by red cell turnover and is therefore a more accurate reflection of glycaemic control in these patients [15].

Iron deficiency with anaemia (IDA) and without anaemia (ID) has been associated with increased prevalence of both diabetes and prediabetes without a concomitant increase in blood glucose, while other anaemias showed a decrease in HbA1c [16]. Insight into the mechanism was recently obtained by the observation that malondialdehyde, which is increased in patients with iron deficiency anemia enhances the glycation of hemoglobin [17]. Alternative measures of glycemic assessment (e.g., glucose monitoring) must be used in the presence of significant iron deficiency anemia, at least until the iron deficiency has been successfully treated. Glycated albumin and fructosamine which reflect glycated serum proteins that are not affected by red blood cell half-life or by ID or IDA may be preferable [18, 19].

The impact of ID on HbA1c may be greatest in pregnancy where it is thought to be a cause for the rise in HbA1c that is seen from the middle to the end of pregnancy. The global incidence of hyperglycaemia in pregnancy in women between 20 and 49 has been estimated to be about 16.9% with a disproportionate number of women from low to middle income countries affected [1]. Appropriate diagnosis and monitoring is critical for tight glucose control which prevents adverse outcomes such as intrauterine death, foetal macrosomia and its attendant complications. Some studies suggest that GA is superior to HbA1c for monitoring diabetes in pregnancy as it reflects more immediate blood glucose and it is not affected by anaemia. The GA Study Group of the Japanese Society of Diabetes and Pregnancy analyzed the association between outcomes (neonatal complications and birth weight) and indicators of glycemic control (HbA1c and GA). In neonates the incidences of neonatal hypoglycemia, polycythemia, respiratory disorders and large for gestational age were found to be significantly higher in the group of women with GA of more than 15.7% compared to those women with GA < 15.7%. In comparison, there was no significant increase in the incidence in the group of women with HbA1c of more than 5.7% compared with the group of women with HbA1c of 5.7% or less [20] which suggests that GA is preferable. While it may be better than HbA1c for monitoring diabetes it does not appear to perform better than HbA1c when used for screening [21].

Chronic Renal Failure

The relationship between HbA1c and glucose control in patients with CKD is affected by wide variability in haemoglobin, poor nutritional status and chronic

inflammation. KDOGI guidelines recommend HbA1c in patients with renal failure as a marker of glycaemic control to delay or prevent microvascular complications [22]. However data from several studies suggest that the correlation between blood glucose levels and HbA1c in patients with chronic kidney disease (CKD) or end stage renal disease (ESRD) may be unreliable [23, 24]. It may be lowered due to shortened erythrocyte lifespan as well as an increased ratio of immature erythrocytes following the administration of erythropoietin. It is also affected by iron therapy and by the use of blood transfusions. Interference from carbamylated haemoglobin may be a contributing issue with immunoassays but not with other methods [25]. Freedman et al. [26] measured HbA1c and GA in subjects on peritoneal and haemodialysis and non-nephropathy controls and showed that while mean glucose levels and GA were higher in patients on dialysis, HbA1c was paradoxically lower. They also showed that HbA1c was inversely associated with estimated glomerular filtration rate (GFR) in advanced CKD, but GA was not significantly associated with GFR [27]. These differences appear to translate to outcomes, as higher GA concentrations, but not HbA1c, have been associated with the development of cardiovascular disease in diabetic patients [28] and as a predictor of predicted mortality and cardiovascular morbidity [29]. A recent study evaluated GA and FA as alternatives to HbA1c in detecting glycemic control among diabetic hemodialysis patients using continuous-glucose-monitoring (CGM)-derived glucose as reference standard. Among diabetic hemodialysis patients, GA was a stronger indicator of poor glycemic control assessed with 7-day-long continuous glucose monitoring when compared to FA and HbA1c [30]. In a German study that looked at outcomes using HbA1c and GA, high GA measurements were consistently associated with increased mortality in patients with diabetes mellitus [31]. So while the data on outcomes is limited what we have so far suggests that elevated GA may be a better of poor outcomes than HbA1c.

A limitation of FA is the falsely low levels when there is rapid albumin turnover such as nephrotic syndrome and liver disease. Glycated albumin is preferred to FA in clinical conditions that result in protein loss such as nephrotic syndrome, liver, and thyroid disease [32].

HIV and Tuberculosis

HIV infection and treatment is associated with insulin resistance and increased risk for T2D [33]. Studies suggest that HbA1c underestimates diabetes in HIV infected people due to shortened red cell lifespan, chronic kidney disease or the use of medication including nucleoside reverse transcriptase inhibitors [19]. Duran et al. [19] reported that,

particularly among individuals living with HIV with lower hemoglobin levels, measured HbA1c values were lower than calculated HbA1c values derived from fructosamine measurements, suggesting that the measured HbA1c values underestimated glycaemia. However, this was not limited to just those with severe anemia. Since many such individuals are treated with medications or affected by conditions that disrupt the erythrocyte lifespan, HbA1c may not be the best marker for assessing glycaemic control in these individuals. Tuberculosis, another important co-morbidity of HIV is also associated with diabetes mellitus. It is estimated that there are more patients with TB and T2D than with TB and HIV; furthermore TB in diabetics is associated with poorer outcomes [34]. Despite World Health Organization guidance that all TB patients should be screened for DM, most facilities in Africa that manage TB patients do not currently perform screening for DM, due in part to the cost and complexity involved. Diabetes screening is further complicated by the presentation of transient hyperglycemia in many TB patients, as well as differences in diabetes risk factors such as body mass index between TB patients and the general public. Data from our center suggests that HbA1c overestimates T2D in patients with TB [35]. Similar findings have been reported from Cape Town and Tanzania [36, 37] While both FA and GA may be suitable alternatives because they are not affected by BMI or anaemia there are no studies that have looked at their performance in patients with TB.

Ethnic Differences

Racial differences in HbA1c levels have been consistently reported in adults and children with type 1 and T2D, with black persons having higher HbA1c levels than non-Hispanic white persons [38–40]. A recent meta-analysis showed that, in individuals without diabetes, HbA1c values were higher in Blacks, Asians; and Latinos when compared to Whites [41]. Whilst the higher HbA1c levels may reflect poorer glycaemic control in Africans it has been hypothesized that this may be the result of race based differences in glycation. If the latter is true, it would mean that HbA1c on average overestimates the mean glucose concentration in black persons. Putative mechanisms for these differences include differences in erythrocytes survival, variations in the glycation gap, heterogeneity in the glucose concentration gradient across the erythrocyte membranes and differences in the passage of glucose mediated by GLUT transporters into the erythrocyte [42]. Persons with higher HbA1c levels than is expected from their serum glucose levels have been termed as “high glycaters” and to those with lower-than-expected A1C as “low glycaters”. Though protein glycation is a non-enzymatic reaction dependent on

glucose concentrations, intracellular enzymatic deglycation of proteins has also been identified and a polymorphism of the key deglycating enzyme, fructosamine-3-kinase, has been suggested to influence HbA1c variability [43].

South Asian ethnicity has been associated with higher HbA1c concentrations, higher fructosamine levels and lower fasting plasma glucose concentrations compared to Caucasians [44] and, among those without diagnosed diabetes, African-Americans had lower fasting and 2 h glucose levels but higher mean levels of HbA1c than whites [45]. The clinical significance of this is uncertain as ethnicity does not appear to modify the association between HbA1c, GA or fructosamine and complications [46].

Body Mass Index

Haemoglobin A1c is positively correlated to BMI while GA is inversely related to BMI in both diabetic as well as in euglycaemic subjects [47, 48]. The inverse correlation between BMI and GA has been attributed to ongoing chronic inflammation in obesity, as GA has been associated with increased CRP in obese individuals [49]. Another possible mechanism is decreased insulin secretion, and subsequent increased post-prandial postprandial hyperglycemia. Koga et al examined correlations between GA and BMI, C-reactive protein (CRP), homeostasis model assessment for β -cell function (HOMA- β) and homeostasis model assessment for insulin resistance (HOMA-R) among T2D. Multivariate analysis showed that HOMA- β was a significant explanatory variable for GA, while CRP and HOMA-R were not. This may be as a result of decreased insulin secretion with increased post-prandial glucose and thus GA reflects the increased post prandial glucose [49]. The negative correlation between BMI and GA raises the possibility that glycated albumin, as a diagnostic test, may be more effective in the nonobese than in obese individuals. Sumner et al. [50] showed that amongst healthy African immigrants in the United States, as individual tests, HbA1c, fructosamine, and GA detected $\leq 50\%$ of Africans with prediabetes. However, combining HbA1c with GA identified nearly 80% of Africans with prediabetes. They also showed that GA outperformed HbA1c for the diagnosis of prediabetes in non-obese individuals, but that in obese individuals HbA1c was superior [51]. It may be that both these tests have a complementary role in screening for diabetes in African patients [52].

Intermediate Glucose Control

Glycated albumin levels rise faster than HbA1c because of its high glycation speed (about 4.5 times that of Hb), and its half-life in serum. Thus it is more useful as an indicator of glycemic status in all those conditions requiring short-term control of changes in glycaemia, such as after the start or modification of diabetes treatments. GA is also a better indicator of post-prandial hyperglycaemia than HbA1c [53].

Diabetic Complications

Albumin is more sensitive to glycation than other proteins because of its high concentration, long half-life and the large number of lysine and arginine residues that may be involved in the formation of early and advanced glycation. Glycated albumin may induce irreversible damage in the different organs and tissues that are the main targets of complications in diabetes mellitus such as the kidneys and retina.

Glycated albumin is involved in the activation and aggregation of platelets; it upregulates the expression of adhesion molecules involved in the formation of atherosclerotic plaques, like ICAM-1 and VCAM-1, and promotes the generation of increased reactive oxygen species [54].

A growing body of evidence suggests that increased GA concentrations are associated with diabetic complications. In a subgroup of subjects from the DCCT, HbA1c and GA were highly correlated and GA paralleled HbA1c over the course of the study. In addition, both HbA1c and GA were associated strongly with progression of retinopathy and nephropathy [30]. More recently Selvin et al. [55] showed that FA and GA were strongly associated with incident diabetes and its microvascular complications, with prognostic value comparable to HbA1c in adults attending the Atherosclerosis Risk in Communities (ARIC) study. They also evaluated associations of FA and GA with risk of coronary heart disease, ischemic stroke, heart failure, and mortality. They noted that elevated baseline concentrations of FA and GA were significantly associated with each of the outcomes even after adjustment for traditional cardiovascular risk factors; with especially strong associations in persons with diabetes mellitus and that these associations were similar to those observed for HbA1c [56].

Conclusions

Both FA and GA are intermediate glycaemic markers because albumin has a half-life of 21 days as opposed to HbA1c which is dependent on erythrocyte life span of 120 days. They are therefore useful when short term assessment of glycaemic status is required such as at the start of treatment, or when treatment is changed. Because they are not affected by anaemia they are useful both in pregnancy and in anaemic patients. This is particularly relevant in middle and low income countries given the high prevalence of anemia.

Glycated albumin appears to be a better indicator of post-prandial glucose, which may be a better indicator of cardiovascular risk. In addition as discussed it may serve as a complimentary marker with HbA1c in prediabetes.

The major limitation to their use is that there are no large scale clinical trials that have investigated the efficacy of GA or FA either for monitoring or for the diagnosis of diabetes. As a consequence reference ranges and cut-off levels are poorly defined. Fructosamine methods have been automated, but not so for GA. Furthermore GA is affected by albumin metabolism and we do not know how chronic infections modify GA. It has been shown to be superior to HbA1c in identifying prediabetes in non-obese individuals. Whether this can be translated to clinical practice remains to be determined. The single study from S Africa that has looked at oral glucose tolerance test, HbA1c, GA and fructosamine showed that abnormal glucose tolerance in a mixed ancestry population was overwhelmingly expressed through 2-h glucose's abnormalities; and no combination of FPG, HbA1c and fructosamine was effective at accurately discriminating OGTT-defined abnormal glucose tolerance [57]. With the massive numbers of prediabetes and diabetics expected it is not feasible to screen using OGTT. It is time for a large scale trial of the optimal screening methods for diabetes across Africa.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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